

Medicinal Chemistry Support for Drug Discovery Grant Applications



Domainex is a Drug Discovery, Contract Research Organisation (CRO) which specialises in working with academics to convert their ideas and discoveries into new treatments for patients. Our in-house technologies are ideal for supporting early stage projects from hit identification and lead optimisation up to candidate selection. We have an impressive track record with three client projects currently in clinical trials.

Through our extensive involvement in previous Grant Applications, we have built up considerable experience of the selection process used by Grant Administrators. Our team's involvement in applications that have progressed through the whole process and been funded means that we have a detailed understanding of the written guidelines and how the selection process works, as well as an excellent appreciation of what the Grant Administrators are looking for.

Accessing Domainex's Expertise

There are a number of ways that Domainex can support your Grant Application.

We can provide advice to applicants in a number of areas and critique both preliminary and full applications, including:

1. Biological rationale of your application, and what the panel is likely to be looking for
2. How appropriate are the project objectives and milestones
3. Medicinal chemistry programme (we have written this section for those applicants who are biology specialists).
4. Screens and the screening cascade
5. Role and selection of external advisors
6. Organisational structure of the project and allocation of responsibilities
7. Budgets and resources – what may be deemed reasonable and necessary?

We can also attend meetings and presentations with the Grant Administrators in order to support your application as it proceeds through the selection process. Post-funding, Domainex can support the programme by providing medicinal and/or computational chemistry services, and by the provision of an 'expert project advisor' if required.

Examples of the service packages we offer include:

Package 1: read preliminary proposal, critique both structure of programme and format of application in terms of the Grant Administrators expectations; one day service

Package 2: as package 1, plus a critique of the science behind your proposal and accessing key literature as required; two day service

Package 3: as package 2, plus writing medicinal chemistry component of preliminary proposal; four to ten days (depending upon amount of background work required).

Package 4: attend meeting at Grant Administrators Head Quarters: one day.

Domainex's Medicinal Chemistry Expertise

Critical to the success of a grant application is to be able to demonstrate that your CRO is able to efficiently and successfully drive the drug discovery programme from target to clinical candidate. Domainex has a unique and trusted formula that rapidly progresses the programme through a series of key drug discovery disciplines that will effectively progress a target through hit identification, hit to lead expansion, and lead optimisation. Domainex has an unrivalled track record of success in producing clinical candidates using this unique formula. Details of each discipline are described in the following sections.

Selection of compounds for screening

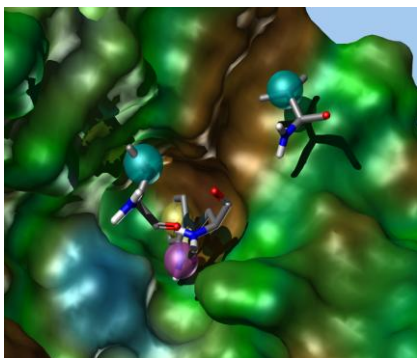
LeadBuilder is the proprietary lead generation platform that has been developed by Domainex to provide unusually rapid and cost-effective access to high-quality hits. As such, it is particularly well-suited to the needs of emerging biotechnology and pharmaceutical companies. This technology integrates our state-of-the-art capability in three key areas: compound collection design and selection; protein modelling; and virtual screening. *LeadBuilder* encapsulates many aspects of our scientists' expertise in successful drug-hunting.

Within *LeadBuilder* we have a database ("NICE") of commercially available compounds that have been carefully selected to meet all of our criteria for an "ideal" screening hit, so that they have several potential points of interaction with a target protein; very favourable molecular properties; and are predicted to have good ADME and toxicity profiles. We are able to interrogate NICE, or any other appropriate compound database, with virtual screens that we can develop from knowledge of our partner's target protein, and/or known ligands. In the event that a target protein

Medicinal Chemistry Support for Drug Discovery Grant Applications



structure is not available, we are able to identify surrogate proteins based upon active-site similarity and use these to develop a model of the active site of the target for virtual screening and design purposes.



Advised by Domainex *LeadBuilder*, our partner can then acquire the compounds that they should screen in whatever quantity or format they need, or we can liaise with the suppliers on their behalf. Our aim is to provide the project with quality hits by selecting what is absolutely relevant to the target from the universe of diverse, relatively cheap, commercially available compounds, whilst saving the time and expense of building a large screening collection.

The key benefits of the *LeadBuilder* platform are:

- Significantly enhanced hit rates in compound screening
- High-quality hits, which are amenable to rapid progression
- Time and cost savings by comparison with other approaches to screening
- "Information rich" hit-to-lead medicinal chemistry programmes

Creating a portfolio of information on compounds

Efficient drug discovery requires that an assessment of synthetic accessibility, chemical stability, drug-likeness, likely toxicology, 'patentability', and many other issues should be made. Domainex has the computing and database tools that are required to provide a wealth of background information on compounds that might be purchased or synthesized. Our chemists have years of experience of creating drug candidates from screening hits, and so they are able to make a highly-informed choice of which

compounds should be further investigated, and which to reject. This allows us to focus more quickly on the best molecules, saving time and reducing overall costs. Thus Domainex can provide assistance with:

- Novelty Assessment - structure-based searches of patent databases and chemical literature databases provide information on where the 'freedom to operate' in this chemical series would lie.
- Synthetic Accessibility - an indication of the ease of synthesis gained through database searching and disconnection analysis.
- Drug-likeness - over the last few years medicinal chemists have been able to define much more accurately the physicochemical properties of a drug molecule relevant to the likelihood of success as a development candidate. Domainex has predictive tools that allow us to make an assessment of which compounds are most likely to be drug-like.

Hits-to-leads

The hit-to-lead process takes the compounds arising from biological screening, and refines these to identify those compounds that represent valid leads. This process includes:

- Confirmation of the active structure.
- Reproducibility of the screening activity.
- Confirmation of the activity of the compound – Domainex can assist with the design of biological assays and provision of standard compounds.
- Stability, Selectivity and Toxicology – appraisal of a hit structure by an experienced medicinal chemist with access to relevant databases gives a valuable insight into the possible metabolic fates of a compound, any chemical instability issues, and whether any functional groups are associated with toxicological problems. Information on the likely cross-over into other activities seen with similar molecules can also be identified.
- Synthesis of analogues to establish preliminary SAR, and to achieve the levels of potency and selectivity required of a lead compound.

Lead Optimisation

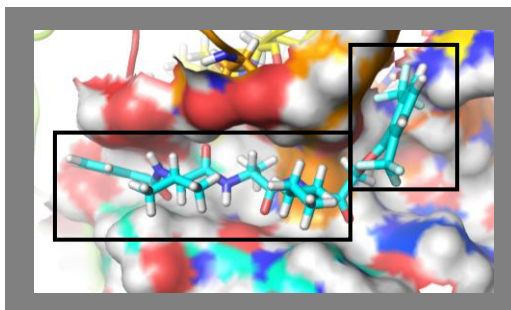
Domainex can design a medicinal chemistry programme around lead compounds. The ability

Medicinal Chemistry Support for Drug Discovery Grant Applications



to use a combination of thoughtful design with one-at-a-time synthesis and the preparation of intelligently designed arrays of compounds in an automated fashion is integral to the way Domainex works, and allows faster provision of higher quality development candidates. Some of the key elements in a typical medicinal chemistry programme include:

- Generation and testing of pharmacophore hypotheses.
- Experimental Design techniques used to plan the synthesis of sets of analogues specifically designed to develop robust structure-activity relationships (SAR) for the series.
- Design of arrays of analogues that explore several areas of the molecule simultaneously, and take into account predicted physicochemical parameters
- Incorporation of protein-ligand structural information (when available) into the library design
- Careful consideration given to absorption, distribution, metabolism and excretion (ADME) properties of compounds throughout the optimisation stage of lead progression.



Lead Development

Compounds emerging from an optimisation process as outlined above are already of high value. Domainex has first-hand experience of further developing these candidates in preparation for pre-clinical and clinical studies and has access to a comprehensive suite of

validated contract research organizations (CROs) to assist with development of the product. In concert with these CROs we can provide assistance with:

- Synthesis scale-up and GMP manufacture
- Optimisation of drug formulation
- Development of standardized, GLP analytical methods
- Detailed pharmacokinetic evaluations
- Toxicological evaluation
- Preparation of regulatory applications

Intellectual Property

Domainex can help with IP planning, and as progress is made with the drug discovery programme, Domainex continually reviews the patent strategy. We are very pro-active in protecting the project intellectual property, working closely with patent agents to assist with timely filings. In any medicinal chemistry programme, Domainex assigns all of the intellectual property to the funding partner.

Our Track Record

Domainex has helped many of its partners to realise their drug research goals, including the delivery of clinical candidates, successful *in vivo* proof of concept experiments, and funding milestones.

Examples of our successes include:

Integrin Antagonists

- Weak screening hits were developed to compounds that delivered positive proof-of-concept results in animals.
- The Client raised €1.4million to finance further R&D based upon these data.

Growth Factor Receptor Antagonists

- Structural analysis of the native ligand led to the design and synthesis of short peptidic inhibitors (4-7mers).
- Modelling of these inhibitors and the binding site has led to the design of novel small-molecule peptidomimetic antagonists, which are currently under optimisation.

Kinase Inhibitors

- Domainex has carried out programmes on a range of kinases for several clients.

Medicinal Chemistry Support for Drug Discovery Grant Applications



- These have been driven by a combination of screening, structure-based design, and inspiration taken from the structures of competitor molecules.
- We have routinely generated compounds that are active in enzyme and cellular assays, leading to patent filings.

Cysteine Protease Inhibitors

- Domainex defined the drug discovery strategy, and co-authored successful and pending grant applications.
- Our modelling and medicinal chemistry has led to the identification of highly-active peptide-based and peptidomimetic inhibitors that display *in vivo* efficacy.
- These are currently in lead optimisation.

Anti-thrombotics

- Domainex designed and synthesised a series of novel anti-thrombotic agents.
- A compound from this series is currently in clinical trials.

Ion Channel blockers

- Domainex devised and implemented a medicinal and computational chemistry strategy for the Client.
- We invented a compound currently in clinical trials.

Contact Details



If you would like to learn more about Domainex's Medicinal Chemistry capabilities, please contact our Research Director:

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